

Applicant : Silviu Itescu  
U.S. Serial No. : 10/693,480  
Filed : October 23, 2003  
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Action and Supplemental Information Disclosure Statement

#### **REMARKS**

Claims 35, 37, 43, 46, 47, 49-51, and 57 are pending in the subject application. In this Amendment, applicant has herein amended claim 35.

Support for amended claim 35 may be found, *inter alia*, in subject application at page 4, lines 3-10 and page 22, lines 10-12.

Accordingly, applicant maintains that this Amendment does not involve new matter, and respectfully requests entry of this Amendment. Upon entry of this Amendment, claims 35, 37, 43, 46, 47, 49-51, and 57 will be pending and under examination in the subject application.

#### **Withdrawn Rejections**

In the September 15, 2011 Office Action, the Examiner on pages 2-3 withdrew the rejection of claims 35, 37, 43, and 57 under 35 U.S.C. §103(a) over Peterson and Hung et al. The Examiner also withdrew the rejection of claim 47 under 35 U.S.C. §103(a) over Peterson and Hung et al., in view of Rempel et al. The Examiner further withdrew the rejection of the claims 49-51 under 35 U.S.C. §103(a) over Peterson and Hung et al., in view of Isner et al.

#### **Obviousness-Type Double Patenting Rejections**

##### **1. U.S. Patent No. 7,662,392 B2**

In the September 15, 2011 Office Action, the Examiner rejected claims 35, 37, 43, 46, 47, 49-51, and 57 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 7,662,392 B2 (the "'392 Patent"). The Examiner asserted that although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a method of treating a disorder comprising administering stromal-derived factor-1. The Examiner also asserted that the pending claims and the claims of the '392 Patent recite administration of SDF-1 to the same subject population and to the same tissue. The Examiner stated that simply stating a new property of SDF-1 does not render the claimed method of the instant application unobvious over the claims of the '392 Patent.

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Applicant's Response

In response, applicant will consider filing a Terminal Disclaimer over U.S. Patent No. 7,122,178 should the claims of the subject application otherwise be deemed allowable.

2. U.S. Serial No. 12/657,264

In the September 15, 2011 Office Action, the Examiner provisionally rejected claims 35, 37, 43, 46-47, 49-51, 57, 69, 70, and 72-79 on the ground of nonstatutory obviousness-type double patenting over claims 69, 70, 72-75, 77, and 78 of copending U.S. Serial No. 12/657,264.

Applicant's Response

As an initial matter, applicant notes that claims 69, 70, and 72-79 are not pending in the subject application. Further, claims 69, 70, 72-75, 77, and 78 of copending U.S. Serial No. 12/657,264 have not been allowed. Accordingly, as set forth in M.P.E.P. §804(I)(B)(2) the provisional rejection over claims 69, 70, 72-75, 77, and 78 of copending U.S. Serial No. 12/657,264 should be withdrawn if the claims of the subject application are otherwise allowable.

Claims Rejected Under 35 U.S.C. §103

In the September 15, 2011 Office Action, the Examiner rejected claims 35, 37, 43, 46, 47, 49-51, and 57 under 35 U.S.C. § 103(a) as allegedly unpatentable over Isner et al. (WO 99/45775), Watanabe et al. (Basic Res. Cardiol., 1998, 93:30-37), and Rempel et al. (Clin. Can. Res., 2000, 6:102-111).

The Examiner alleged that Isner et al. teach methods for inducing angiogenesis in ischemic tissue of a patient in need of such treatment by administration of vascularization modulating agent. The Examiner also alleged that Isner et al. teach that the vascularization modulating agent may be SDF-1. The Examiner further alleged that Isner et al. teach that the disclosed method may be used to prevent or treat ischemic cardiomyopathy, cerebrovascular ischemia, and myocardial ischemia; and that administration of the agent may be intramuscular. The Examiner acknowledged on page 8 of the September 15, 2011 Office

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Action that Isner et al. do not disclose intramyocardial or intracoronary administration of SDF-1.

The Examiner alleged that Watanabe et al. disclose administration of growth factors as a new therapeutic approach for the enhancement of collateral vessel formation in the ischemic heart. The Examiner also alleged that Watanabe et al. disclose that a growth factor, FGF-2 (or bFGF), is injected alone or with heparin or heparin sulfate into normal myocardium and the border zone of ischemic myocardium in a porcine myocardial infarct model. The Examiner further alleged that Watanabe et al. disclose that in the ischemic border zone area, an increase in the density of arterioles is observed in the FGF-2 alone group, FGF-2 plus heparin, and FGF-2-coated heparin bead groups as compared with control.

Finally, the Examiner alleged that Rempel et al. disclose that human SDF-1 gene encodes two isoforms, SDF-1 $\alpha$  and SDF-1 $\beta$ , which arise from alternative splicing and differ only in that SDF-1 $\beta$  contains four additional 3' amino acids.

The Examiner alleged that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of administering SDF-1 to a subject suffering from ischemic cardiomyopathy, cerebrovascular ischemia, and myocardial ischemia as taught by Isner et al. by intramyocardially administering human SDF-1 $\alpha$  or SDF-1 $\beta$  as taught by Rempel et al. and Watanabe et al. The Examiner also alleged that the person of ordinary skill in the art would have been motivated to make the modification in order to localize angiogenesis or induction of collateral vessels to the ischemic heart of the patient. The Examiner further alleged that the person of ordinary skill in the art would have expected success because similar angiogenic growth factors were already being intramyocardially administered to the heart at the time the invention was made; and SDF-1 $\alpha$  and SDF-1 $\beta$  are isoforms encoded by the SDF-1 gene.

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Applicant's Response

In response, applicant respectfully traverses the Examiner's rejection for reasons detailed below. As explained below, the cited prior art teach systemic administration of the particular vascularization agent claimed, i.e. SDF-1. Additionally, the conflicting prior art as a whole shows confusion in the field about whether intramyocardial administration of a vascularization agent is effective. Therefore, the cited references neither teach a method involving "intramyocardially or intracoronarily administering to the subject an amount of an agent comprising a human stromal derived factor-1", as recited in the pending claims, nor provide a basis to reasonably expect such a method to be successful.

Isner et al. disclose a method for increasing vascularization in a mammal which comprises administering an effective amount of a vascularization agent, including GM-CSF, VEGF, SLF, SCF, SDF-1, G-CSF, HGF, Angiopoietin-1, Angiopoietin-2, M-CSF, b-FGF, and FLT-2 ligand. (Paragraph bridging pages 4-5.) In particular, Isner et al. disclose that subcutaneous administration of GM-CSF mobilizes endothelial progenitor cells (EPCs), which can then migrate to a site of ischemia and enhance neovascularization. (Page 27, line 26 - page 28, line 4; page 37, lines 28-31) Therefore, Isner et al. disclose that systemic (i.e. subcutaneous) administration of vascularization agents, such as GM-CSF, is required to mobilize EPCs which then migrate to a site of ischemia to enhance neovascularization.

Isner et al. do not differentiate between various vascularization agents. Isner et al. do not teach or suggest that SDF-1 could or should be administered differently than GM-CSF. Also importantly, Isner et al. do not teach or suggest that different methods of administration could lead to improved results. According to Isner et al. relatively simple systemic administration is equivalent in terms of result to a more complex administration. Accordingly, Isner et al. do not provide any reason for a person of ordinary skill in the art to seek out complex intramyocardial or intracoronary administration of any of its vascularization agents.

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Watanabe et al. disclose effects of intramyocardial administration of FGF-2, in the presence and absence of heparin, on angiogenesis in a porcine model of myocardial infarction. (Page 30, Abstract) Therefore, Watanabe et al. only disclose a specific method for administering a particular vascularization agent, FGF-2. The relation of FGF-2 to the claimed agent, SDF-1, is unclear except that both are vascularization agents.

Rempel et al. disclose that SDF-1 gene encodes two isoforms, SDF-1 $\alpha$  and SDF-1 $\beta$ . Rempel et al. do not disclose any method for administering SDF-1.

#### No Reasonable Expectation of Success Based On Cited References

There is no evidence of record showing that the teaching of Watanabe et al., e.g. intramyocardial administration of FGF-2, could be generalized to all vascularization agents. Therefore, a person of ordinary skill in the art at the time could not reasonably determine whether other vascularization agents, such as any of those disclosed in Isner et al., would have similar effects as FGF-2 when administered intramyocardially.

#### Confusion About Effects of Local Administration

Furthermore, Hung et al. (U.S. Patent Application Publication No. 2003/0171294 A1), a reference previously cited by the Examiner, disclose that intracoronary administration of FGF-2 is ineffective.

Hung et al. taught that administration of FGF polypeptide to the ameroid model provided no benefit over placebo. See Figures 7-9 of Hung et al., wherein data labeled as "IC" represents results obtained from intracoronary administration of FGF polypeptide to the ameroid model. (Data labeled as "low", "mid", and "high" in Figures 7-9 of Hung et al. represents results obtained from administration of FGF polypeptide to the hibernating myocardium model, which is not representative of a disorder of a heart tissue involving loss or apoptosis of cardiomyocytes.) Applicant explained in the Amendment filed July 18, 2011 that the ameroid model disclosed in Hung et al. is a model characterized by loss or apoptosis of cardiomyocytes. ("[The]

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100% occlusion that is provided by the ameroid model makes the ameroid model more analogous to a myocardial infarction", Page 6, [0039])).

Whereas Hung et al. show that intramyocardial or intracoronary administration of FGF polypeptide is not effective for treating a disorder of a heart tissue involving loss or apoptosis of cardiomyocytes, Watanabe et al. show that intramyocardial administration of FGF-2 could increase the number of arterioles in infarct border area. Consequently, a person of ordinary skill in the art would understand that these references to at best evidence confusion in the art about the effects of intramyocardial administration of FGF-2.

MPEP 2141.02 provides that "Ascertaining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole." Additionally, MPEP 2143.01(II) provides that "[t]he test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts. Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another."

The teaching of Hung et al. conflicts with the teaching of Watanabe et al. Watanabe et al. disclose that the number of arterioles were increased both in normal myocardium and infarct border area with intramyocardial administration of FGF-2. However, Watanabe et al. also disclose that the number of capillaries were not affected by the treatment of FGF-2. (Page 30, Abstract) Hung et al. show in an actual animal model that intramyocardial or intracoronary administration of FGF polypeptide is not effective for treating a disorder of a heart tissue involving loss or apoptosis of cardiomyocytes. Therefore, weighting all the teachings in the prior art, a person of ordinary skill in the art is likely to understand that a disorder of a heart

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tissue involving loss or apoptosis of cardiomyocytes may not be treatable by intramyocardial administration of a vascularization agent, FGF-2, which is consistent with the teaching of Hung et al. while not inconsistent with the teaching of Watanabe et al.

Contribution of the Subject Application

Applicant respectfully directs the Examiner's attention to the Specification of the subject application which, *inter alia*, discloses that:

intramyocardial administration of SDF-1 causes improvement in cardiac function after acute ischemia through two separate mechanisms, a direct mechanism which involves induction of cardiomyocyte cycling and regeneration and an indirect mechanism operating through enhanced chemotaxis of mobilized bone marrow-derived endothelial progenitors and cardiac neovascularization. (Page 78, lines 21-27)

The subject application thus discloses two distinct methods for administering SDF-1 to improve cardiac function. Prior to applicant's disclosure of the direct mechanism of SDF-1, and in view of Isner et al.'s disclosure of a systemic method (indirect mechanism) to enhance neovasucularization, a skilled artisan would not have had any motivation to administer SDF-1 intramyocardially or intracoronarily. Moreover, a skilled artisan could not have had a reasonable expectation of success of intramyocardial or intracoronary administration of SDF-1 based on the conflicting results from intramyocardial administration FGF-2 disclosed in Watanabe et al. and Hung et al.

Accordingly, applicant respectfully submits that the combination of Isner et al., Watanabe et al., and Rempel et al. does not render obvious the pending claims. Applicant requests that the Examiner reconsider and withdraw this rejection.